REMARKS

This amendment responds to the office action mailed March 27, 2003. Minor amendments have been made to the specification on page 19. As the amendments to the specification are fully supported by the specification as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested.

Claims 1-20 were pending in the instant Application. With the instant amendment, Claims 1 and 11 have been amended to correct minor informalities. As the amendments to the claims are fully supported by the specification and Claims 1 and 11, as originally filed, they do not constitute new matter. Entry thereof is therefore respectfully requested. After entry of this amendment, the pending claims are: claims 1-20.

Applicants expressly reserve the right to pursue any canceled subject matter in one or more related, continuation, divisional or continuation-in-part application(s).

I. THE OBJECTION TO THE SPECIFICATION

A. The Use of the Trademarks

The specification has been objected to because allegedly the trademarks "ABI" and "Dionex" should be capitalized and should be accompanied by generic terminology.

Applicants submit that upon entry of the instant amendment, the terms "ABI" and "Dionex" in the specification are deleted in order to expedite prosecution and avoid possible unnecessary use of trademarks. Such deletion should not affect proper identification of the products referred to in the specification, since they are identified by name and manufacturer. Therefore, Applicants respectfully request that the objection to the specification be withdrawn.

B. Sequence Listings and Sequence Identifiers

The specification is objected to for failing to comply with the requirements of 37 C.F.R. §§ 1.821 through 1.825. Applicants submit herewith a Sequence Listing for SEQ ID NOS:1-4 of the specification. The PTO further asserts that the primers disclosed on pages 26-33 and 35 require SEQ ID NO identifiers.

Applicants respectfully note that MPEP § 2422.03 provides that it is "generally acceptable to present a single, general sequence in accordance with the sequence rules and to discuss and/or claim variants of that general sequence without presenting each variant as a

separate sequence in the 'Sequence Listing.'" The MPEP provides this guidance to minimize complexity in the Patent Office's sequence database.

Applicants submit that the primers disclosed on pages 26-33 and 35 are mere variants of the primers having the sequences of SEQ ID NOS:1-4 of page 18 of the specification. For example, the first primer of page 26, designated 2'omeG, is a variant of SEQ ID NO:3 having a 2'-O-methyl-guanosine at replacing the guanosine nucleotide at its 3' terminus (*see* page 19, lines 1-10). Since the primers of pages 26-33 and 35 are variants of SEQ ID NOS:1-4, Applicants respectfully submit that these variants do not require individual SEQ ID NO identifiers according to MPEP § 2242.03.

Applicants respectfully request that the objection to the specification under 37 C.F.R. § 1.821 -1.825 be withdrawn.

II. CLAIM OBJECTIONS

Claims 1 and 11 stand objected to for a minor informality. Applicants submit that amended Claims 1 and 11 lack this informality. Accordingly, Applicants respectfully request that the objections to Claims 1 and 11 be withdrawn.

III. REJECTIONS UNDER 35 U.S.C. § 103

Claims 1-4, 6-8, 10-14, 16-18 and 20 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Will, 2001 (U.S. Patent No. 6,001,611, "Will") in view of Gold *et al.*, 2000 (U.S. Patent Publication No. 2002/0172962 A1, "Gold"). Further, Claims 5, 9, 15 and 19 stand rejected under 35 U.S.C. § 103(a) as being allegedly unpatentable over Will in view of Gold, in further view of Reese (WO 00/56747, "Reese"). Applicants respectfully traverse these rejections on the grounds that the PTO has failed to establish a *prima facie* case of obviousness against any of the claims.

A. The Legal Standard

To reject claims in an application under 35 U.S.C. § 103, the Patent Office bears the initial burden of establishing a *prima facie* case of obviousness. *In re Bell*, 26 USPQ2d 1529, 1530 (Fed. Cir. 1993); MPEP § 2142. In the absence of establishing a proper *prima facie* case of obviousness, Applicants who comply with the other statutory requirements are entitled to a patent. *In re Oetiker*, 24 USPQ2d. 1443, 1444 (Fed. Cir. 1992). In order to establish *prima facie* obviousness, three basic criteria must be met.

First, the prior art must provide one of ordinary skill in the art with a suggestion or motivation to modify or combine the teachings of the references relied upon by the PTO to arrive at the claimed invention. When an obviousness determination relies on one reference, there must be suggestion or motivation to modify the teaching of the reference in the manner suggested by the PTO. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). Alternatively, when an obviousness determination relies on a combination of two or more references, there must be some suggestion or motivation to combine the references. *WMS Gaming Inc. v. International Game Technology*, 51 USPQ2d 1385, 1397 (Fed. Cir. 1999). The suggestion or motivation to combine the references generally arises in the references themselves, but may also be inferred from the nature of the problem or occasionally from the knowledge of those of ordinary skill in the art. *See id.* The mere fact that references could be modified or combined does not render the resultant modification or combination obvious unless the prior art also suggests the desirability of the modification or combination. *In re Mills*, 16 USPQ2d 1430 (Fed. Cir. 1990); MPEP § 2143.01.

Second, the prior art must provide one of ordinary skill in the art with a reasonable expectation of success. Thus, the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531 32 (Fed. Cir. 1988).

Third, the prior art, either alone or in combination, must teach or suggest each and every limitation of the rejected claims. *In re Gartside*, 53 USPQ2d 1769 (Fed. Cir. 2000). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991). If any one of these criteria are not met, *prima facie* obviousness is not established, and Applicants are not required to show new or unanticipated results. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985).

B. <u>The Rejection of Claims 1-4, 6-8, 10-14, 16-18 and 20</u>

Claims 1-4, 6-8, 10-14, 16-18 and 20 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Will in view of Gold. As discussed in Section A above, in order to establish *prima facie* obviousness, the PTO must cite a suggestion or motivation in the art to modify or combine references to arrive at Applicants' invention and must show that the prior art provides one of ordinary skill in the art with a reasonable expectation of success of the suggested combination. Applicants respectfully submit that the references cited by the PTO are not sufficient to establish a *prima facie* case of obviousness against Claims 1-4, 6-8, 10-

14, 16-18 and 20 because the PTO has failed to meet its burden of demonstrating the required motivation and reasonable expectation of success to combine the teaching of Will and Gold.

Independent claims 1 and 11 recite a kit and a method respectively, for carrying out a nucleic acid amplification reaction comprising, *inter alia*, a pair of primers, wherein at least one primer of said pair contains a modified nucleotide within the three 3' terminal nucleotide positions. The modified nucleotide is selected from 2'-O-methyl nucleotides, 2'-fluoro-nucleotides, 2'-amino nucleotides and arabinose nucleotides. Claims 2-4, 6-8, and 10 depend from claim 1 and claims 12-14, 16-18 and 20 depend from claim 11.

The PTO acknowledges that Will does not teach or suggest the use of 2'-O-methyl nucleotides, 2'-fluoro-nucleotides, and 2'-amino nucleotides in its nucleic acid reaction. However, the PTO asserts that because Gold teaches 2'-O-methyl nucleotides, 2'-fluoro-nucleotides, and 2'-amino nucleotides, it would have been *prima facie* obvious to apply Gold *et al*'s modified nucleotides to Will's kits and methods for carrying out a nucleic acid amplification reaction.

Applicants respectfully remind the PTO that in order to make out a *prima facie* case of obviousness there must be some suggestion or motivation, either in the references or in the knowledge available to one of ordinary skill in the art to modify the references or to combine the reference teachings. The teaching or suggestion and the expectation of success must both be found in the prior art and not based on Applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ.2d 1438 (Fed. Cir. 1991). Applicant submit that, contrary to what the PTO asserts, the PTO has provided no motivation to combine Will and Gold.

First, the PTO has not provided any motivation for using a nucleotide modified on its sugar instead of on its base in Will's methods. In Will, the modified nucleotides are modified on their base, comprising a modifier group covalently bound to the nitrogen atom of an exocyclic amine on a base (Will col. 8, line 20-45, and claim 1-7). Will teaches that the modifier group *on the base* sterically hinders base pairing, thus reducing non-specific amplification (Will, col. 10, line 40 - col. 11, line 18).

In contrast, Gold's modified nucleotides include 2'-O-methyl nucleotides, 2'-fluoro-nucleotides and 2'-amino nucleotides. All cited modified nucleotides of Gold are modified on their sugar, containing a bulky side group bound to C-2 of the sugar (page 9, lines 10-20 and page 11, lines 7-12, *i.e.*, paragraph number 36 and 43 of U.S. Patent Publication No. 2003/00448171A1). Gold teaches the use of said modified nucleotides for purposes unrelated to a nucleic acid amplification reaction. In particular, Gold teaches the use of said modified nucleotides to synthesize RNA molecules that have reduced affinity for HIV-RT

and are resistant to enzymatic and chemical degradation (Gold, page 10, paragraph number 104, page 13, paragraph number 138, page 16, paragraph number 163 and page 17, paragraph number 168). Applicants note that nowhere does Gold even mention a nucleic acid amplification reaction. Applicants submit that the PTO has provided no evidence that one of skill in the art would select nucleotides modified at the sugar for use in Will's methods. Applicants submit instead that when looking for substitution for modified nucleotides in Will's methods, one of ordinary skill in the art would select those nucleotides with ability to interfere with base pairing according to Will, *i.e.*, those with modified bases.

The PTO asserts that in order to obtain a greater yield of the intended amplification product while reducing non-specific amplification, one of ordinary skill at the time the invention was made would have been motivated to apply Gold's modified nucleotides to Will's kits and methods. However, the PTO has not provided any evidence that such motivation for one of skill in the art to select nucleotides modified on their sugar rather than on their base as taught by Will.

Applicants therefore respectfully submit that the PTO has not provided sufficient motivation for one of ordinary skill in the art at the time the invention was made to apply Gold's modified nucleotides to Will's kits and methods.

Even assuming, *arguendo*, that the cited references may have suggested applying Gold's modified nucleotides to Will's kits and methods for carrying out a nucleic acid amplification reaction, which they do not, the PTO has provided no evidence that one of ordinary skill in the art would have had a reasonable expectation that the combination suggested by the PTO would succeed. Given that Gold's nucleotides are modified on the sugar backbone instead of on the base, the PTO has not provided any evidence that Gold's modified nucleotides would possess the same properties or function in the same way as those modified nucleotides in Will's kits do. Particularly, on one hand, the PTO has failed to provide any evidence that applying Gold's modified nucleotides to Will's methods would reduce, rather than increase non-specific amplification. In fact, the PTO has not provided any evidence in Will or Gold or in the art that Gold's modified nucleotides would have any effect on non-specific amplification at all. On the other hand, if applying Gold's modified nucleotides to Will's methods were to reduce non-specific amplification, the PTO has also failed to show any evidence that Gold's modified nucleotides would not preclude primer extension entirely.

Applicants respectfully remind the PTO that it is the specification of Applicants' instant patent application, not the art, that demonstrates modified nucleotides such as Gold's

reducing non-specific amplification and allowing intended amplification. Specifically, Applicants' specification shows that the side group bound to the sugar in Gold's modified nucleotides, sterically interferes with the binding of DNA polymerase to the primer-target complex (page 11, lines 7-12, *i.e.*, paragraph number 36 and 43 of U.S. Patent Publication No. 2003/00448171A1). Such interference delays the initial primer extension, thus reducing non-specific amplification; at the same time, such interference is not enough to preclude primer extension for the primer-target duplex (page 10, line 50 - page 11, line 6, *i.e.*, paragraph number 40-42 of U.S. Patent Publication No. 2003/00448171A1). Moreover, Example 3 and Example 4 demonstrate that using modified primers containing 2'-O-methyl nucleotides, 2'-fluoro-nucleotides, or 2'-amino nucleotides indeed reduces non-specific amplification and still yields the intended amplification product under amplification conditions.

In addition, even if Gold's modified nucleotides might be effective at reducing non-specific amplification, the PTO has failed to provide any evidence that said nucleotides will be effective within the three 3' terminal nucleotide positions in a modified primer as recited in the claims. As discussed in Section A above, in order to establish *prima facie* obviousness, the PTO must show that the skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the PTO would succeed. *In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). By also failing to make such a showing, the PTO has failed to establish *prima facie* obviousness against Claims 1-4, 6-8, 10-14, 16-18 and 20.

As there is no motivation or suggestion to combine the teachings of Will and Gold, and as there is no reasonable expectation that the combination would succeed, the PTO has failed to establish a *prima facie* case of obviousness against independent claims 1 and 11. Claims 2-4, 6-8, and 10 depend from claim 1 and claims 12-14, 16-18 and 20 depend from claim 11. The references are therefore not sufficient to establish a *prima facie* case of obviousness against Claims 1-4, 6-8, 10-14, 16-18 and 20.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 1-4, 6-8, 10-14, 16-18 and 20 under 35 U.S.C. § 103(a) as being obvious over Will in view of Gold be withdrawn.

C. <u>The Rejection of Claims 5, 9, 15 and 19</u>

Claims 5, 9, 15 and 19 stand rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Will in view of Gold and in further view of Reese. Applicants respectfully

submit that the Patent Office has failed to meet the burden of demonstrating the required motivation and reasonable expectation of success to combine the teachings of Will, Gold and Reese, thereby failing to establish *prima facie* obviousness against Claims 5, 9, 15 and 19.

Independent claims 1 and 11 recite a kit and a method respectively, for carrying out a nucleic acid amplification reaction comprising, *inter alia*, a pair of primers, wherein at least one primer of the pair contains a modified nucleotide within the three 3' terminal nucleotide positions. Claims 5 and 9 depend from claim 1 and claims 15 and 19 depend from claim 11. Claims 5, 9, 15 and 19 recite that said modified nucleotide is an arabinose nucleotide; Claims 9 and 19 recite that the arabinose nucleotide is at the 3'terminal position of the primers.

The PTO relies on the combination of Will and Gold to establish *prima facie* obviousness against independent claims 1 or 11 from which Claims 5, 9, 15 and 19 ultimately depend. The PTO acknowledges that neither Will nor Gold teaches the use of arabinose nucleotides. However, the PTO states that Reese teaches arabinose nucleotides and alleges that one of skill in the art would have been motivated to apply Reese's modified arabinose nucleotides to Will's and Gold *et al*'s combined kits and methods.

The PTO has not provided any motivation to apply Reese's arabinose nucleotides to Will's modified nucleic acid amplification reaction. Like 2'-O-methyl nucleotides, 2'-fluoro-nucleotides and 2'-amino nucleotides, arabinose-containing nucleotides are modified on their sugar when compared to nucleotides of naturally occurring nucleic acids. In particular, the orientation of the -H and -OH side groups of the C-2 of arabinose is altered when compared to ribose or deoxy-ribose sugars. As discussed in section B above, the PTO has failed to provide any motivation for using a nucleotide modified on its sugar instead of on its base in Will's methods. Applicants submit that Reese does not provide the necessary motivation. Reese teaches a process for the preparation of arabinose nucleotides. Reese does not teach or suggest anything about using arabinose nucleotides or any nucleotides with modified sugars in a nucleic acid amplification reaction, much less in Will's methods. Neither does Reese teach or suggest that arabinose nucleotides in particular or nucleotides with modified sugars in general, might interfere with base pairing or reduce non-specific amplification. Accordingly, Reese cannot provide the missing motivation to apply Reese's arabinose nucleotides to Will's modified nucleic acid amplification reaction. Applicants therefore submit that the PTO cannot combine the teachings of Reese and the teachings of Will and Gold to establish a *prima facie* case of obviousness against dependent Claims 5, 9, 15 and 19.

Next, the PTO has failed to show that there is a reasonable expectation of success to apply Reese's arabinose nucleotides to Will's methods. The PTO has not provided any

evidence that Reese's arabinose nucleotides used in Will's modified nucleic acid amplification reaction would have any effect on reducing non-specific amplification. Further, even if Reese's arabinose nucleotides were effective at reducing non-specific amplification, the PTO has failed to show that Reese's arabinose nucleotides would not preclude primer extension entirely for a primer-target hybridization duplex under amplification conditions. Lastly, the PTO has failed to provide any evidence that Reese's arabinose nucleotides would function within the three 3' terminal nucleotide positions in a modified primer instead of at other positions in the primer.

Applicants therefore submit that even in view of Reese, the PTO has failed to provide the requisite motivation and reasonable expectation of success to apply Reese's arabinose nucleotides to Will's modified nucleic acid amplification reaction. Accordingly, Applicants submit that the PTO has not established a *prima facie* case of obviousness against dependent Claims 5, 9, 15 and 19.

In view of the foregoing, Applicants respectfully request that the rejection of Claims 5, 9, 15 and 19 under 35 U.S.C. § 103(a) as being obvious over Will in view of Gold in further view of Reese be withdrawn.

CONCLUSION

In light of the above amendments and remarks, Applicants respectfully submit that Claims 1-20 satisfy all the criteria for patentability and are in condition for allowance. Applicants request that the PTO reconsider this application with a view towards allowance and solicit an early passage of Claims 1-20 to issuance. The PTO is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

No fee in addition to the extension fee is believed due with this Amendment. However, pursuant to 37 CFR § 1.136(a)(3), the Commissioner is authorized to charge all required fees, fees under 37 CFR § 1.17 and all required extension of time fees, or credit any overpayment, to Pennie & Edmonds, LLP U.S. Deposit Account No. 16-1150 (order no. 1803-311-999).

Respectfully submitted,

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